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(54) Enteric coated solid pharmaceutical unit dosage forms

(57) A medicament-containing core of a solid unit dosage form is provided with an enteric coating by applying (e.g. in a coating pan) an aqueous solution of a water soluble salt of a cellulose partial ester of a dicarboxylic acid, the aqueous solution being free from organic solvent, until an enteric coating around each medicament core has been built up. The salt may be a sodium or ammonium salt of hydroxypropyl methyl cellulose phthalate or cellulose acetyl phthalate.

GB 2 057 876 A

SPECIFICATION

Enteric coated solid pharmaceutical unit dosage forms

This invention relates to enteric coated solid pharmaceutical unit dosage forms, e.g. tablets, dragees and capsules.

Such enteric coated unit dosage forms have a uniform controlled amount of a medicament in a coated unit dosage medicament core, the medicament core being, for example, a tablet core or a capsule containing a therapeutically effective dose of the medicament, for example, as a powder or liquid. The coating remains intact when in contact with gastric juices thereby preventing escape of the medicament when the unit dosage form passes through the stomach. The coating disintegrates sufficiently when in contact with intestinal juices thereby permitting the medicament to be leached by the intestinal juices. The medicament then acts in the intestines or is absorbed through the walls of the intestinal tract. Various *in vitro* tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopeia of several countries.

As used herein, the term "enteric coated" or "enteric coating" refers to a coating which remains intact (showing no disintegration or cracking of the coating) for at least 1 hour in contact with HCl of pH 1.2 at 36 to 38°C and thereafter distintegrates within 60 minutes when the pH is raised to 6.8, e.g. in a KH_2PO_4 buffered solution.

Cellulose derivatives are well-known and universally accepted coating materials for medicament cores. Cellulose partial esters, e.g. cellulose acetate phthalate (hereinafter referred to as CAP) and hydroxy - propyl methyl cellulose phthalate (hereinafter referred to as HPMCP) are universally accepted materials for enteric coatings. Hitherto suitable coating processes for applying these cellulose derivatives onto medicament cores were based on organic solutions. Such processes suffer from several disadvantages. Firstly the solvents are generally inflammable so special storage vessels for the solvents are required. Secondly in admixture with air the solvents can be explosive so special safety precautions are required. Thirdly pollution hazards associated with toxic organic solvents may exist, so special equipment for dispersing or scrubbing the exhaust gases is required. Fourthly the amount of any toxic organic solvent remaining in the coating has to be carefully monitored. Fifthly the organic solvents are costly. It has been proposed to use aqueous-organic solvent systems and for non-enteric coatings using water soluble cellulose derivatives it is possible to use a purely aqueous system on a commercial scale.

Various proposals hav been put forward to eliminate organic solutions also for enteric coating with cellulose partial esters. For example according to U.S.S.R Author's Certificate No 374082 published in June 1973 in the name of Leningrad Antibiotics Research Institute, tabl ts in a fluidized bed coater are spray coated in three steps: firstly by an aqueous solution of an ammonium salt of CAP, secondly by a hydrophobic wax such as a plant oil and thirdly again by an aqueous solution of an ammonium salt of CAP.

It was clearly essential to have the wax layer in order to obtain an enteric coating.

Zhitomirskii et al in Khimiko Farmatsertic heskii Zhurnal Vol 7(8) August 1973 pp 46-49 teaches that the fluidized bed technique is more advantageous than the coating pan technique and apparently contemplates coatings produced in fluidized bed coaters using aqueous solutions of ammonium salt of cellulose acetyl phthalate and shellac in conjunction with hydrophobic wax-fatty undercoats. However, in fact the coating pan technique has certain advantages over the fluidized bed technique, e.g. it causes less tablet abrasion and coating material loss, it requires smaller volumes of drying air and thus lower energy supplies, and it is cheaper to run.

In another proposal according to DOS 2524813 published in 1976 in the name of Shinetsu a two step coating process is described. In the first step mediament cores are said to be coated by an aqueous solution of a water soluble salt of a cellulose partial ester in a fluidized bed coater or in a pan coater. In the second step the coated medicament core is treated with an acid in order to produce an enteric coating by converting the cellulose ester salt coating back into the insoluble acid form. The second step is clearly shown to be necessary to produce an enteric coating as each coated medicament core subjected to the coating step but not to the subsequent acid treatment step was stated not to have an "enteric" coating as the medicament core disintegrated completely or had most of the contents dissolved out in the presence of gastric fluid in the disintegration test for uncoated tablets in accordance with U.S. Pharmacopeia 18 Revision. The acid treatment is, however, costly, tedious and difficult to effect in a commercial scale. It can lead to medicament being leached out during the acid wash and may destroy any acid-sensitive medicament present.

According to Japanese Application No 2918/1977 in the name of Toyama, extensive studies were conducted to improve the drawbacks of the Shinetsu process. The solution proposed, however, was to employ at least 5% of a miscible organic solvent in an HPMCP or CAP coating solution. The use of an organic solvent is undesirable. Recently Shinetsu (see e.g. Technical Information H-20 dated January 21, 1979 and Technical Information H-23 dated February 20, 1979) have proposed using an aqueous dispersion of HPCMP in the presence of triacetin as an enteric coating technique.

The dispersion, however, must be continuously stirred during the coating operation, and even then pistol blockages tend to occur. Moreover, the HPMCP should be in the form of a v ry fine p wder and an undercoat, .g. Pharmacoat 606, is required.

Thus, there has be n a real need f r providing an nteric coating with cellulose esters in purely aqueous solvents, especially in pan coaters, but there is no simple accepted solution capable of commercial us .

We have now surprisingly found that, despite what is said in DOS 2524813, if the spraying condi-

tions are carefully monitored to prevent ruptures and abrasion of the coatings being formed, it is possible even when the unit dosage forms are coated in intimate contact in a coating pan, to obtain simply a solid unit dosage having an enteric coating form wherein the enteric characteristics of said coating is imparted essentially by one component only, namely a water soluble salt of a cellulose partial ester of a dicarboxylic acid. The acid treatment step called for by DOS 252813 is no longer necessary.

The present invention accordingly provides in one aspect a process for producing an enteric coating on a medicament core of a solid unit dosage form which comprises coating the medicament cores with an aqueous solution of a water soluble salt of a cellulose partial ester of a dicarboxylic acid, the aqueous solution being completely free from any, or significant amounts of, an organic solvent, until such time as an enteric coating around each medicament core has been built up.

It is to be appreciated that the coating with the cellulose partial ester that alone provides the enteric coating. No other enteric coating, e.g. of a hydrophobic material such as wax, shellac, plant-oil, need be provided. Any conventional coater is suitable, (see J. F. Pickard et al. Manufacturing Chemist and Aerosol News, May 1974, p. 42), e.g. a fluidized bed coater or preferably a coating pan. If desired, a ventilated sugar coating pan or a modified sugar coated pan (e.g. a Pellegrini Type with a dipsword, available from Pellegrini, Italy or Glatt, BRD) may be used. Preferably the coating pan is perforated and side-vented, e.g. machines such as Accela Cota, Manesty, England or the Hi-Coater, Vector Corporation, USA.

The coater may be fitted with spray pistols. Suitable spray pistols are those used for other aqueous coating systems, e.g. compressed air pistols having a nozzle diameter of from about 0.5 to about 1.8 mm for coating pans.

The enteric coating may be applied in conventional manner for the application of analogous cellulose esters, e.g. hydroxypropyl methyl cellulose, from purely aqueous solutions to similar unit dosage forms in the same environment and machine. The process parameters can vary between wide limits from environment to environment, machine to machine and day to day and depend on, *inter alia*, the pan load, pan speed, baffling system present, application rate, drying air input and exhaust rate, temperature of the drying air, relative humidity, core variation, viscosity of spraying solution, degree of atomization, spray profile etc.

It is most important that the process parameters which could effect the quality of the coating, and e.g. lead to ruptures, must be carefully and continuously monitored and adjusted for optimum coating conditions during the coating process according to procedures well known in the art, in particular avoiding running the process anywhere near to being too w t r too dry.

For example, frictional wear between the coated medicament cores themselves as well as with th sides of the coater causes abrasion of the coating n the prominent parts (e.g. edges) of the dosage form, and reduces thickness of the film edges without exposing the cores. This abrasion is the result of the process being run too dry, and may be overcome e.g. by increasing the spray rate or decreasing the temperature differences between incoming and exhaust air. Sticking of the coated medicament core on the sides of the coater or to each other (stacking) with the resultant formation of imperfections (e.g. micro-blisters) in the coatings, as a result of the process being run too wet, may be overcome e.g. by decreasing the spray rate or increasing the temperature difference between incoming and exhaust air.

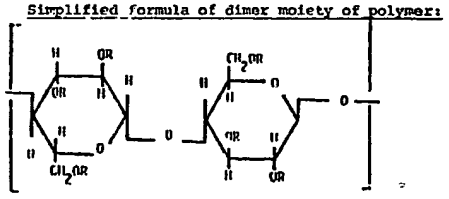
The effects of running the process too dry (abrasion) or too wet (sticking) may not be observable by eye from the coated medicament core. The effects can, however, be observed when the cores are magnified or when they are brought into contact with simulated gastric juices or HCl at pH 1.2. The film thickness reduction at the edges of the medicament core due to abrasion, and lifting of the film, without necessarily leaving a hole, on the faces of the medicament core, due to sticking may also be seen.

Preferred cellulose partial esters are those of succinic acid, maleic acid or preferably phthalic acid. The cellulose ester may bear additionally monocarboxylic ester groups, e.g. acetyl or may be partially etherified, e.g. have methoxy or 3 - hydroxypropoxy groups present.

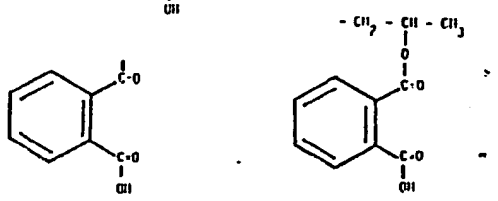
Suitable cellulose partial esters include cellulose acetate phthalate and preferably hydroxypropyl methyl cellulose phthalate. Examples of the former are HP50 and HP55 obtainable from Shinetsu, Tokyo, Japan and an example of the latter is the brand CAP obtainable from Eastman Kodak, Rochester, N.Y., USA.

Hydroxypropyl methyl cellulose phthalate may be characterised as follows:–

Simplified formula of dimer moiety of polymer:



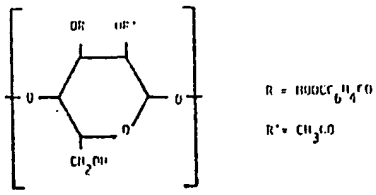
R:- H, - CH_3, - CH_2 - CH - CH_3 (OH)



Composition	HP 50	HP 55
Phthalyl content%	20-27	27-35
Hydroxypropoxy cont nt%	7-18	6-10
Methoxy content %	20-25	18-22

The above mentioned cellulose ac tate phthalat is characteris d as follows:–

Structural formula of monomer moiety of polymer:



Composition

Mixed partial ester of cellulose with 30-40% Phthalyl groups, 17-23% Acetyl groups and maximal 6% free acid groups calculated as phthalic acid.

If desired more than one cellulose partial ester may be used. A suitable mixture comprises hydroxypropyl methyl cellulose phthalate and cellulose acetate phthalate, e.g. in a weight ratio of from 20:1 to 60:1.

The salt form may be suitably the triethanolamine salt, preferably the ammonium salt and especially the sodium salt. The salt form may be made in conventional manner, by reaction of the cellulose partial ester with appropriate or equivalent quantities of the base in water until a solution occurs.

The coatings may for example be applied from an aqueous solution having a viscosity of from about 5 to about 240 cps, as determined in a Brookfield viscometer at 20°C. Generally this corresponds to a 5 to 20% (%$_w$) solution of the cellulose partial esters.

Naturally the coating solution may contain other conventional pharmaceutical excipients which will be incorporated into the enteric coating. Suitably these comprise from 0.005 to 30%, more suitably from 0.01 to 10%, of the coating solution. For example dyestuffs such as water soluble amaranth and/or pigments such as red iron oxide, erythrosin, or titanium dioxide may be present in an amount of for example about 0.1 to about 1% of the coatings. Anti-sticking agents or fillers such as talc may be present in an amount of up to 25% of the enteric coating. Plasticisers may be present, e.g. dioctyl phthalate, or preferably triacetin, in an amount of up to about 50% of the enteric coating, or polyethylene glycol in an amount of up to about 5% of the enteric coating. Controlled amounts of polymers which affect the break-down of the coating in gastric and intestinal juices may be present in the coating solution. Generally these may be present in a concentration of up to 5%, e.g. 0.1 to 5%, of the solution and up to 30% of the enteric coating. Appropriate polymers include synthetic polymers soluble in aqueous acids such as polyethylene glycol, polypropylene glycol, polyvinylpyrrolidone, semi-synthetic polymers soluble in aqueous acids, e.g. hydroxypropyl cellulose (such as Klucel LF), hydroxypropyl methyl cellulose (Pharmacoat E 15), synthetic polymers insoluble in aqueous acids such as poly (vinyl acetat -co- crotonic acid) natural polymers insoluble in aqueous acids such as alginic acid and its salts, and semi-synthetic polymers insoluble in aqueous acids e.g. carboxymethyl cellulose.

Any excipient in the coating solution is preferably added in quantities, and a form, e.g. a salt form when the salt is solubl but the acid not, consistent with maintaining an adequately low viscosity solution for producing a film coating.

It is to be appreciated that the enteric coating may be provided as a single layer of uniform composition or may be provided as multiple layers of different compositions, e.g. each containing a water soluble salt of a cellulose partial ester and one layer containing a pigment.

In general a film coating of from 0.045 mg to 0.65 mg per sq millimeter of solid unit dosage form (0.035 to 0.5 mm thick) will provide a satisfactory enteric coating, but thicknesses outside this range may also provide satisfactory coatings.

The resistance of the coating to gastric juices naturally increases with the coating thickness.

Coated medicament cores prepared according to the process of the invention may be prepared which satisfy more stringent standards for enteric coatings than those indicated above, e.g. the standards laid down in e.g. Japan Pharmcopeia VIII and Pharmacopeia Europe I.

Thus coatings which show no visible softening or cracking within 2 hours in gastric juices have been prepared. Naturally the medicament may still be leached out in gastric juices even though the coating remains intact. In general for enteric coatings it has been observed in *in vitro* tests with HCl of pH 1.2 that less than 20 percent of the medicament is leached out within 1 hour. Coatings have been made that leach out less than 10% or 5% of the medicament within 2 hours.

The coatings produced by the process of the invention are at least as stable as equivalent coatings produced from organic solvents of cellulose partial esters. For example, propyphenazone tablets coated with aqueous solutions of the sodium or ammonium salt of HPMCP and the sodium salt of CAP were prepared and stored for 12 months at 25°C. In all cases the amount of propyphenazone leached out of tablets after storage for 12 months after 2 hours contact with HCl at pH 1.2 was similar to, or up to 60% less than, the amount leached out of the tablets before storage. Satisfactory maintenance of the coating has also been observed for tablets stored at 35° for 6 months.

The medicament cores may be any suitable medicament core for a unit dosage form.

Whilst the process of the invention may be applied to coating capsules, e.g. capsules each moulded in one piece, it is preferred to be applied to tablet cores. The tablet cores should be of a size that can be coated satisfactorily in the coating pan used. Suitable tablet cores may be, for an Accela Cota, from about 3 mm upwards in diameter e.g. from about 50 mg each to about 1000 mg each.

The coated unit dosage forms may then be dried in known manner and packed e.g. into blister packs. Optionally before packing the dosage form may be coated with a further non-enteric lay r which may contain medicament. Thus, for example, an outer layer containing medicament for immediat release into the stomach may be press-coated onto the coated medicament c re.

Any medicament present in the medicament c re optional outer medicament layer may be any medi-

cament e.g. one which acts in the intestines or is absorbed through the intestines. Examples of suitable medicaments include analgesics, antibiotics, anti-histamines, tranquillizers, myotonolytics, enzymes, cardiac agents, beta and/or alpha-blockers, vasoconstrictors, hypotensives, vasodilators, neuroleptics and anti-depressants.

The medicament may be, for example, an ergot alkaloid, e.g. ergotamine, dihydroergotamine, codergocrine, or bromoergocryptine. Other examples include diclofenac sodium, pindolol, phenylpropanolamine, or acid-sensitive enzyme preparations.

Any pharmaceutical excipient conventionally used for the unit dosage form contemplated may be used in the medicament core and any outer layer present.

The present invention also covers unit dosage forms produced by the process of the invention and provides, in another aspect, a method of providing release of a medicament in the intestines which comprises enterally administering the medicament in the form of an enteric coated solid unit dosage form according to the invention. Thus the invention provides a method for providing the sustained action of a medicament if this is slowly released from the core or slowly absorbed through the intestinal walls, or a method of protecting medicaments which are sensitive to gastric juices during passage through the stomach.

The following examples illustrate the invention. In the Examples the following abbreviations are used:–

HPMCP is the hydroxypropyl methyl cellulose phthalate brand HP 50 produced by Shinetsu.

CAP is cellulose acetate phthalate produced by Eastman Kodak,

PEG 6000 is polyethylene glycol having a molecular weight of about 6000,

PVP is polyvinylpyrrolidone, brand Kollidon 30, with a mean molecular weight of about 28000,

Triacetin is glycerin triacetate,

Amaranth is water soluble amaranth,

Kelacid is a brand of alginic acid,

CMC is carboxymethyl cellulose, brand Hercules 7LF,

HPC is hydroxypropyl cellulose brand Klucel LF,

HPMC is hydroxypropylmethyl cellulose, brand Pharmacoat E 15.

All the components used herein have characteristics as described in "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete" by H. P. Fiedler, Edito Cantor KG 1971, which lists the names of suitable suppliers.

EXAMPLE 1: Spray Solution

The water insoluble cellulose ester is reacted with an appropriate base to bring it into water soluble form. Examples of various spray solution compositions are given in the following table, in which the amounts of compositions ar giv n in g per charge.

Medicament cores

The tablet cores (235 mg ach) had the following compositions:–

Component	*Weight (mg)*
Propyphenazone	24
Lactose	162.23
Corn Starch	40.07
Polyvinylpyrrolidone	4.47
Magnesium stearate	1.79
Talc	2.44

The tablet components were granulated according to known procedures and compressed to form cores of 9 mm diameter, having bevelled edges, and upper and lower weakly concave sides (radius of curvature 18-20 mm).

Coating method

10 kg of the above tablet cores were loaded into a 24 inch rotating perforated drum coater (Accela Cota).

The spraying conditions were as follows:–

Drum rotation speed: 16 r.p.m.
Inlet air quantity: ca 3000 m^3/h.
Exhaust air quantity: ca 3200 m^3/h.
Inlet air temperature: 56-60°
Outlet air temperature: 34-40°
Temperature difference between inlet and exhaust air ca 20-22°C.
Spray Pistol: Binks 2 step type 2610.
Nozzle No 63; Needle No 363; Cover No 63 PB; openings 10 to 20.
Nozzle diameter: 0.7 to 1.8 mm.
Distance of nozzle from cores; ca 15 to 30 cm.
Spray pressure: 3 atmospheres.
Solution pumped by a 4-finger pump at 35 to 60 r.p.m. Finger pump arm diameter ca 5 cm. Finger pump tubing: 4 to 8 mm diameter,
Spray programme: Spray 60 secs.
Spray interval 2 secs.
Total coating time: 4.25 to 5.5 hours.

Enteric disintegration test:

A group of 6 tablets were treated with HCl pH 1.2 at 37° for 2 hours and observed. The results are shown in the table as an indication of the aspect of the coat after the treatment. + indicates an intact film; – indicates a non-intact film.

The state is indicated as follows:–

S = Solid
F = Firm

The tablets were then transferred to a KH_2PO_4 pH 6.8 solution at 37°C. The time taken for disintegration of the coat was taken. The maximum or average time in minutes is given in the table along with a standard deviation, if available.

Component,						
Cellulose ether	a	b	c	d	e	f
HPMCP	1242	1552.5	1242	1552.5	776.3	1552.5
CAP	–	–	24.8	31.1	–	–
Base						
NaOH	79.5	99.4	83.8	104.8	–	–
NH_4OH (25%)	–	–	–	–	98.5	197.1
Additives						
Amaranth	1.24	1.55	1.24	1.55	0.77	1.55
Water, ad	9940	12420	9940	12420	6210	12420
Enteric disintegration test						
Aspect after HCl	F+	S+	F+	F+	F+	S+
Disintegration time (pH 6.8)	<20	<20	<20	<20	<20	<20

EXAMPLE 2:

Gillazym cores were used each weighing 750 mg and of a long, oblong lozenge shape, and containing an acid sensitive enzyme preparation of 300 mg Pancreatin (lipase; amylase; protease), 180 mg dehydrocholic acid and 40 mg dimethylpolysiloxane.

10 kg of the cores were coated in a 24 inch Accela Cota machine and sprayed successively without interruption with three solutions:

I	HPMCP	134.6	g
	NH_4OH (25%)	15.1	g
	Erythrosin	0.067	g
	Water ad	1076	g
II	HPMCP	269.2	g
	NH_4OH (25%)	30.015	g
	Erythrosin	0.135	g
	Talc	50	g
	Titanium Dioxide	47.5	g
	Water ad	2152	g
III	HPMCP	403.8	g
	NH_4OH (25%)	45.2	g
	Erythrosin	0.2	g
	Water ad	3228	g

The speed of rotation of the Accela Cota–because of the large size of tablets and the small drum– had to be carefully monitored to prevent surging with the result that crests of the rolling cores received insufficient solution and ran too dry, and troughs of the rolling cores received too much solution and hence ran too wet. (This surging problem is not encountered with larger Accela Cotas). The drum rotation speed was 16-20 r.p.m. for spraying solution I; and 9-12 r.p.m. for spraying solutions II and III. Pump speed (r.p.m.) = 40 (solution I); 47.5 (II); 55 (III). Inlet air temperature = 59°C. Exhaust air temperature: 40°C. Nozzle setting = 20. The total coating time was 140 minutes; other spraying conditions substantially as for example 1.

The coated Gillazym cores were compared with commercially availabl Gillazym preparation, which are manufactured by applying a HPMCP coating of similar thickness from an organic solution, in the gastric juice resistance test according t US Pharmacopeia XIX.

After application of solutions I and II, the cores coated according to the process of th present inv ntion remained completely intact like the commercial preparation after 60 minutes in contact with simulated gastric juices. An acid penetration of the coating of about 0.4-0.6 mm was observed compared to an acid penetration of about 0.2 to 0.3 mm in the commercial preparation. After application of the third solution III the cores coated according to the invention showed comparable acid penetration to the commercial preparation. The disintegration time of the coating at pH 5.5 was comparable (8-16 minutes) for the Gillazym cores produced according to the invention and for commercial Gillazym preparations.

EXAMPLE 3:

Pindolol/sodium lauryl sulphate cores containing the following components:–

Component	*Weight (mg)*
Pindolol(base)	10
Sodium lauryl sulphate	5
Ethyl cellulose	9
Polyvinylpyrrolidone acetate	5
Microcrystalline cellulose	14
Mannitol	55
Talc	1
Magnesium stearate	1

are prepared as disclosed in DOS 2732335.
10 kg of the cores are coated in analogous manner to that disclosed in Example 1.

Spray solution

Component	*Weight*
HPMCP	807.7 g
NH_4OH (25%)	90.5 g
Erythrosin	0.4 g
Water ad	6380 g

Spray conditions

Drum speed	16 r.p.m.
Inlet air temperature	59°C
Outlet air temperature	36-37°C
Nozzle setting	20
Finger pump speed	72.5 r.p.m.
Coating time	104 minutes

Other conditions as for Example 1.

Disintegration test

This was effected by treating the tablets with simulated gastric juices for 2 hours and then KH_2PO_4

thereafter.

Experiment a): 3 coated cores prepared according to the process of the invention with a 15 mg film (A) and cores coated with HMPCP from organic solutions according to the above-mentioned DOS with an 11 mg film (B) were compared estimating the amount of pindolol released.

The results were as follows:–

Time (minutes)	% Pindolol release (± Standard Deviation) A (invention)		B (known)	
5	1.4	(0.1)	3.2	(0.5)
15	1.4	(0.1)	4.1	(0.9)
30	1.5	(0.1)	6.5	(0.9)
60	1.8	(0.1)	8.2	(1.3)
120	3.2	(0.1)	15.4	(2.8)
pH Change				
150	24	(0.8)	31.4	(4.4)
180	37.8	(6.4)	39.0	(5.2)
200	74.1	(3.2)	72.8	(4.4)

Experiment b): Cores were prepared according to the above process, but having different film thicknesses (C-E).

These were compared to a coated core produced according to the process described in the above DOS with an 11 mg coating (F) applied from organic solutions.

The pindolol release observed in simulated gastric juices was as follows:–

% Pindolol released from Core (Film in mg)

Time minutes	C (5.5 mg)	D (8.25 mg)	E (11 mg)	F (11 mg)
5	0.2	0.96	1.1	1.3
15	0.3	1.1	1.2	1.6
30	0.8	1.4	1.3	2.9
60	4.8	2.8	1.3	6.1
90	8.8	4.5	1.3	9.0
120	11.4	6.7	1.4	13.3

These experiments show that the coatings produced according to the invention are significantly more resistant to gastric juices than coatings produced from organic solvents. The coating also quickly disintegrates in intestinal juices allowing release of the medicament as expected.

EXAMPLE 4:

As described in Example 1 prophyphenazone tablets were coated with the following solutions:–

	Weight g I	II	III
HPMCP	1552.5	1552.5	–
CAP	–	–	700
NaOH	–	29.82	132
NH_4OH 25%	193	–	–
Amaranth	1.55	1.55	0.7
Water to	12420	12420	11200

The tablets were stored for 1 year at 25°C and then treated in the disintegration test in simulated gastric juices for 2 hours and then in simulated intestinal juices thereafter. The values for propyphenazone release were compared to the initial values.

% propyphenazone release

Time (min)	I initial value	I after 1 year	II init. value	II after 1 year	III init. value	III after 1 year
15	4.2	2.5	4.7	1.7	9.0	8.9
30	5.5	3.3	6.5	1.9	11.7	11.7
60	6.2	4.4	8.2	2.2	17.7	17.7
120	7.2	5.7	10.4	3.2	27.4	25.6
pH change						
300	90.6	84.7	90.8	97.3	92.3	94.0

The results indicate that the coatings produced according to the invention are stable and in the case of HPCMP coatings become more resistant to gastric juices with time, whereas in intestinal juices they disintegrate as expected.

EXAMPLE 5:

Optalidon cores of 355mg each were made in analogous manner to that described in Example 1 having the following composition:

Component	*Weight (mg)*
Butalbital	50
Propyphenazone	125
Caffeine	25
Klucel LF	9
Corn Starch	134
Stearic acid	1.0
Talc	6.0

10 kg of the above tablet cores were coated in analogous manner to that described in Example 1 using the solutions listed in the following table (each component amount is given in grams) and effecting the disintegration test as indicated in Example 1.

Component	a)	b)	c)	d)	e)	f)
Cellulose ether						
HPMCP	1080	1350	1850	1552.5	–	1250
CAP	–	–	–	–	1000	–
Base						
NaOH	69.1	86.4	–	99.4	18.8	75
NH_4OH (25%)	–	–	23	–	–	–
Additives						
Amaranth	1.08	1.35	1.85	1.55	1	1.25
Triacetin	–	–	–	–	–	25
Water ad	8640	10800	14600	12420	16000	10000
Aspect after HCl	F	S	S	F	F	S
Disintegration time (pH 6.8)	15	15	12-17	12.3-19.8	7.3-8.5	<15

Component,										
Cellulose ether	g	h	i	j	k	l	m	n	o	p
HPMCP	1437.5	1150	1150	1552.5	1552.5	1552.5	1552.5	1552.5	–	1552.5
CAP	–	–	–	–	–	–	–	–	1000	–
Base										
NaOH	86.3	73.6	73.6	99.4	99.4	99.4	99.4	99.4	188	–
Triethanolamine	–	–	–	–	–	–	–	–	–	372.6
Additives										
Amaranth	1.44	1.15	1.15	1.55	1.55	1.55	1.55	1.55	1.00	1.55
Triacetin	28.75	–	–	–	–	–	–	–	–	–
Alginic Acid (Kelacid)	–	23	–	–	–	–	–	–	–	–
CMC	–	–	144	–	–	–	–	–	–	–
HPC	–	–	–	31	–	–	–	–	–	–
HPMC	–	–	–	–	31	–	–	–	–	–
PVP	–	–	–	–	–	31	–	–	–	–
PEG	–	–	–	–	–	–	31	–	–	–
Titanium dioxide	–	–	–	–	–	–	–	155	–	–
Talc	–	–	–	–	–	–	–	299	–	–
Iron oxide, red	–	–	–	–	–	–	–	63.3	–	–
Water, ad	11500	11500	11500	12420	12420	12420	12420	12420	16000	12420
Enteric disintegration test										
Aspect after HCl	S+	S+	S+	S+	F+	S+	S+	S+	F+	F+
Disintegration time (pH 6.8)	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20

CLAIMS

1. A process for producing an enteric coating on a medicament core of a solid unit dosage forms which comprises coating the medicament cores with an aqueous solution of a water soluble salt of a cellulose partial ester of a dicarboxylic acid, the aqueous solution being completely free from any, or significant amounts of, an organic solvent, until such time as an enteric coating around each medicament core has been built up.

2. A process according to claim 1 wherein the cellulose partial ester is cellulose acetyl phthalate.

3. A process according to claim 1 wherein the cellulose partial ester is hydroxypropylmethyl cellulose phthalate.

4. A process according to claim 1 wherein the enteric coating comprises a mixture of salts of cellulose acetyl phthalate and hydroxypropylmethyl cellulose phthalate.

5. A process according to claim 1, 2, 3 or 4 wherein the sodium salt is present as the salt.

6. A process according to claim 1, 2, 3 or 4 wherein the ammonium salt is present as the salt.

7. A process according to any preceding claim wherein the final enteric coating is from 0.035 to 0.5 mm thick.

8. A process according to any preceding claim wherein the enteric coating is applied as a single layer.

9. A process according to any preceding claim wherein the aqueous solution contains from 5 to 20% by weight of the ester.

10. A process according to any preceding claim wherein the coating is effected in a coating pan.

11. A process according to any preceding claim wherein the medicament core is a tablet core.

12. A process according to claim 11 wherein the coated core is then provided with an outer medicament non-enteric layer.

13. A process for the production of an enteric coated solid unit dosage form substantially as hereinbefore described with reference to any one of

the Examples.

14. An enteric coated solid unit dosage form whenever produced by the process of any one of claims 1 to 13.

15. An enteric coating on a solid unit dosage form produced by coating with a spray of an aqueous solution of water soluble salt of a cellulose partial ester of a dicarboxylic acid, the aqueous solution being completely free from any, or significant amounts of, an organic solvent, until such time as an enteric coating around each medicament core has been built up.

16. A solid unit dosage form having an enteric coating form wherein the enteric characteristic of said coating is imparted essentially by one component only, namely a water soluble salt of a cellulose partial ester of a dicarboxylic acid.

17. A unit dosage form according to claim 16 wherein the cellulose partial ester is cellulose acetyl phthalate.

18. A unit dosage form according to claim 16 wherein the cellulose partial ester is hydroxypropylmethyl cellulose phthalate.

19. A unit dosage form according to claim 16, 17 or 18 wherein the enteric coating comprises a mixture of salts of cellulose acetyl phthalate and hydroxypropylmethyl cellulose phthalate.

20. A unit dosage form according to claim 16, 17, 18 or 19 wherein the sodium salt is present as the salt.

21. A unit dosage form according to claim 16, 17 18 or 19 wherein the ammonium salt is present as the salt.

22. A unit dosage form according to any one of claims 16 to 21 wherein the enteric coating is from 0.035 to 0.5 mm thick.

23. A unit dosage form according to any one of claims 16 to 22 wherein the coating is a single layer of uniform composition.

24. A unit dosage form according to any one of claims 16 to 23 which is a tablet.

25. A unit dosage form according to any one of claims 16 to 24 wherein the medicament is pindolol.

26. A unit dosage form according to claim 25 wherein the enteric coating is surrounded by an outer medicament non-enteric layer.

27. A method of providing the release of a medicament in the intestines which comprises enterally administering the medicament in the form of an enteric coated solid unit dosage form of claim 14 or any one of claims 16 to 26.

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